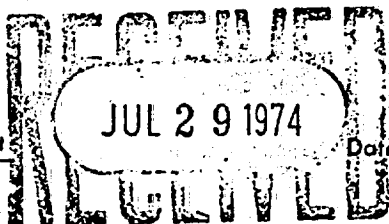


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THE COUNCIL FOR TOBACCO RESEARCH-U.S.A., INC.

110 EAST 59TH STREET  
NEW YORK, N. Y. 10022  
(212) 421-8885

Application for Research Grant  
(Use extra pages as needed)



Date: July, 1974

1. Principal Investigator (give title and degrees):

Victor Havlicek, M.D., D.Sc.  
James C. Haworth, M.B., Ch.B., M.D.  
Victor Chernick, M.D.

2. Institution & address:

University of Manitoba  
Winnipeg, Manitoba

3. Department(s) where research will be done or collaboration provided:

Department of Pediatrics, Health Sciences Centre  
685 Bannatyne Avenue, Winnipeg, Manitoba, Canada

4. Short title of study:

Effect of smoking on the neonatal EEG and subsequent electrical and functional maturation of the brain.

5. Proposed starting date: January 1, 1975

6. Estimated time to complete: 2 years

7. Brief description of specific research aims:

- 1) To determine whether smoking during pregnancy affects brain function at birth as judged by computer analyzed electroencephalography and to correlate the EEG obtained at birth with subsequent intellectual development.
- 2) To determine whether the prognosis, in terms of physical growth, intellectual development and brain electrical activity of surviving children of women who smoked during pregnancy differs from that of children of non-smoking mothers. Also, to determine whether prognosis can be related to the number of cigarettes smoked or to carboxyhemoglobin content of the blood at birth.

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8. Brief statement of working hypothesis:

2.

The association between cigarette smoking during pregnancy and fetal growth retardation has been firmly established although there may be an element of doubt whether this association is causal. The hypothesis that cigarette smoking interferes with brain growth in-utero and therefore subsequent electrical and intellectual development of the child will be tested in a prospective study.

9. Details of experimental design and procedures (append extra pages as necessary)

The Sample of Pregnant Women

The sample will consist of women attending the Women's Centre of the Health Sciences Centre, where there are nearly 4,000 deliveries a year. In order to interview women at several stages of pregnancy, it would be ideal to include the women who attend the prenatal clinic at the hospital. However these patients tend to be those in the lower socioeconomic categories and so as to obtain a proper socioeconomic "mix" it will be necessary to include also women who receive their prenatal care at the offices of practising obstetricians. For practical reasons these women can be interviewed only once - while they are in hospital after the delivery of their babies. It is planned that the sample shall consist of 100 clinic patients and 100 postpartum patients.

The following information will be obtained:

1) Smoking History:

Whether a smoker or a non-smoker, the amount of smoking according to the number of cigarettes smoked per day, change in smoking habits during pregnancy

2) Personal and Obstetric Data:

Age, height, pregravid weight, weight gain during pregnancy, ethnic origin, socioeconomic status (rated according to occupation of the woman or the husband) parity, past and present obstetric history.

The Sample of Infants

The following information will be collected about the infants born to the pregnant women studied: birthweight, gestation, crown heel length, head circumference, apgar score (1 minute and 5 minute), presence of major malformations (as defined by the Medical Records Department, Women's Centre), neonatal disorders. Still births and neonatal deaths will also be recorded.

Cord blood carboxyhemoglobin will be measured in as many babies as possible (those born during normal working hours). This estimation will be performed on the

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## I.L. CO-Oximeter at the Children's Centre.

### The Follow-Up Study

A group of these infants will be selected for the follow-up study. At the moment it is planned to study 100 infants of smoking mothers and an equal number of infants of non-smokers (this is the maximum number that Dr. K. McRae, the Director of the Child Development Clinic, feels that his Department can accommodate). Infants will be selected for follow-up on the following basis:

- 1) The mother smoked more than 10 cigarettes regularly since the 4th month of the pregnancy.
- 2) Follow-up is practical (family lives in or near Winnipeg).
- 3) The mother gives informed consent.

For each index infant selected for follow-up, a control infant will also be selected. The control infant will be the baby born to the next non-smoker who matches the index infant as closely as possible for sex, birthweight and gestational age, and age, parity and socioeconomic class of the mother (all factors which may affect developmental progress). If the mother does not give consent, or if follow-up is impractical, the next born suitable infant will be substituted.

The follow-up procedure for index and control infants will be as follows:

- 1) Computer analyzed electroencephalogram (EEG) during different stages of sleep in the newborn period. Data on normal infants have already been collected (see appended manuscript). EEG's will be repeated at 6, 12, and 24 months of age.
- 2) Attendance at the Child Development Clinic at 6, 12 and 24 months of age. The following information will be documented at each visit: a) physical measurements - weight, height, head circumference, b) neurological abnormalities, and c) developmental assessment (Yale Developmental Schedule based on Gesell early developmental testing technique).

### Data Handling and Analysis

All data will be coded, punched on to computer cards and analyzed according to standard statistical techniques.

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## 10. Space and facilities available (when elsewhere than item 2 indicates, state location):

Space and facilities to undertake this study are available in the Health Sciences Centre. A fully-equipped experimental EEG laboratory is located adjacent to the newborn nurseries. A special Child Development Clinic has been in operation in the Centre since 1959 and they have agreed to undertake the follow-up studies.

## 11. Additional facilities required:

N11

## 12. Biographical sketches of investigator(s) and other professional personnel (append):

## 13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

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14. First year budget:

A. Salaries (give names or state "to be recruited")

Professional (give % time of investigator(s) even if no salary requested)	% time	Amount
Dr. V. Havlicek	10%	N11
Dr. J.C. Haworth	10%	N11
Dr. V. Chernick	5%	N11
Dr. Rima Childeava (Professional Assistant) (Dr. Childeava is essential for this project)	100%	\$12,000

Technical

Clerk-Stenographer - This person is essential for the handling of the records. Specifically she will type questionnaire forms, keep records, code the data, arrange for follow-up visits and type correspondence.

100%	\$ 5,200
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Sub-Total for A \$17,200

B. Consumable supplies (by major categories)

a) paper, computer punch cards, stenographic supplies	\$ 300
b) EEG paper, tape for tape recorder, ink	\$ 700

Sub-Total for B \$ 1,000

C. Other expenses (itemize)

Computer time for analysis of EEG's and statistical work. \$ 1,500

Sub-Total for C \$ 1,500

Running Total of A + B + C \$19,700

D. Permanent equipment (itemize)

Nil (all necessary equipment available)

Sub-Total for D -

E. Indirect costs (15% of A+B+C)

E \$ 2,955

Total request \$22,655

15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	\$18,500	\$1,000	\$1,500	--	\$3,000	\$24,000
Year 3						

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16. Other sources of financial support:

List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Development of the EEG in the Neonatal Period	Department of National Health and Welfare, Canada		July 1, 1974 to June 30, 1975 (terminal award to complete work on neonatal hypoglycemia and the EEG)

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
NIL			

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Drs. V. Havlicek and J. Haworth

Signature V. Havlicek J. Haworth Date           

J. Haworth

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Number

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V. Havlicek

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Responsible officer of institution

Typed Name DR. E. SIRLUCK

Title PRESIDENT UNIVERSITY OF

Signature Dr. E. Sirluck MANITOBA Date JUL 23 1974

Telephone 204 474-9345

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Number

Extension

Checks payable to

Mailing address for checks

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### SELECTED REFERENCES

1. Astrup, P., Trolle, D. Olsen, H.M., Kjeldsen, K.: Effect of moderate carbon-monoxide exposure on fetal development. *Lancet* 2:1220, 1972.
2. Becker, R.F. and King, J.E.: Studies on nicotine absorption during pregnancy. II The effects of acute heavy doses on mother and neonates. *Amer. J. Obstet. Gynec.* 95: 515, 1966.
3. Becker, R.F., Little, C.R.D. and King, J.E.: Experimental studies on nicotine absorption in rats during pregnancy. III Effect of subcutaneous injection of small chronic doses upon mother, fetus and neonate. *Amer. J. Obstet. Gynec.* 100:957, 1968.
4. Butler, N.R., Goldstein, H. and Ross, E.M.: Cigarette smoking in pregnancy: its influence on birth weight and perinatal mortality: *Brit. Med. J.* 2: 127, 1972.
5. Butler, N.R., Goldstein, H.: Smoking in pregnancy and subsequent child development. *Brit. Med. J.* 4: 573, 1973.
6. Cole, P.V. Hawkins, L.H. and Roberts, D.: Smoking during pregnancy and its effects on the fetus. *J. Obstet. Gynaec. Brit. Comm.*: 79:782, 1972.
7. Comstock, G.W., Shah, F.K., Meyer, M.B., Abbey, H.: Low birth weight and neonatal mortality rate related to maternal smoking and socioeconomic status: *Amer. J. Obstet. Gynec.* 111: 53, 1971.
8. Cope, I., Lancaster, P. and Stevens, L.: Smoking in pregnancy. *Med. J. Aust.* 673, 1973.
9. Essenberg, J.M., Schwind, J.V. and Patras, A.R.: Effects of nicotine and cigarette smoke on pregnant female albino rats and their offspring. *J. Lab Clin. Med.*: 25:708, 1940.
10. Frazier, T.M., Davis, G.H., Goldstein, H. and Goldberg, I.D.: Cigarette smoking and prematurity: a prospective study. *Amer. J. Obstet. Gynec.*: 81: 988, 1961.
11. Haddon, W. Jr., Nesbitt, R.E.L. and Garcia, R.: Smoking and pregnancy: Carbon monoxide in blood during gestation and at term. *Obstet. Gynaec.* 18: 262, 1961.
12. Hardy, J.B., and Mellits, E.D.: Does maternal smoking during pregnancy have a long-term effect on the child? *Lancet* 2:1332, 1972.
13. Kullander, S., Kallen, B.: A prospective study of smoking in pregnancy. *Acta. Obstet. Gynec. Scand.* 50:83, 1971.
14. Peterson, W.F., Morese, K.M. and Kaltreider, D.F.: Smoking and prematurity. A Preliminary report based on study of 7740 caucasians. *Obstet. Gynec.* 26:775, 1965.
15. Rantakallio, P.: Groups at risk in low birth weight infants and perinatal mortality. *Acta. Paediat. Scand. Suppl.* 193, 1969.

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16. Russell, C.S., Taylor, R. and Maddison, R.M.: Some effects of smoking in pregnancy. J. Obstet. Gynaec. Brit. Comm.: 73:742, 1966.
17. Russell, C.S., Taylor, R., Law, C.E.: Smoking in pregnancy, maternal blood pressure, pregnancy outcome, baby weight and growth, and other related factors. A prospective study. Brit. J. Prev. Soc. Med. 22:119, 1968.
18. Schoeneck, F.J.: Cigarette smoking in pregnancy. New York State J. Med. 41: 1945, 1941.
19. Simpson, W.J.: A preliminary report on cigarette smoking and the incidence of prematurity. Amer. J. Obstet. Gynec. 73:807, 1957.
20. Sontag, L.W. and Wallace, R.F.: The effect of cigarette smoking during pregnancy upon the fetal heart rate. Amer. J. Obstet. Gynec. 29:77, 1935.
21. Underwood, P.B., Kesler, K.F., O'Lane, J.M. and Callagan, D.A.: Parental smoking empirically related to pregnancy outcome. Obstet. Gynec. 81:988, 1961.
22. Yerushalmy, J.: The relationship of parents' cigarette smoking to outcome of pregnancy--implication as to the problem of inferring causation from observed associations. Amer. J. Epidemiol. 93:443, 1971.
23. Younoszai, M.K., Kacic, A. and Haworth, J.C.: Cigarette smoking during pregnancy: the effect upon the menatocrit and acid base balance of the newborn infant. Canadian Med. Assoc. J. 99: 197, 1968.
24. Younoszai, M.K., Peloso, J. and Haworth, J.C.: Fetal growth retardation in rats exposed to cigarette smoke during pregnancy. Amer. J. Obstet. Gynec. 104:1207, 1969.

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